The General Process of Cancer Clinical Trials and Their Various Phases
Submitted by Dr. Marchello for the December 13, 2011 Cancer Clinical Trials Advisory Council Meeting

I have been asked to review the clinical trial phases which are outlined below as the definitions approved by the National Cancer Institute. If you read this long description, what will be clear is that the phases of clinical research have nothing to do with cost, either to the investigator, to the patient, or to third parties. These definitions are completely based on the science and financial implications of studies would have to be looked at on the basis of each individual study.

Phase 0:

These trial represent the earliest step in testing new treatments in humans. In a Phase 0 trial, a very small dose of chemical or biological agent is given to a small number of people (approximately 10-15) to gather preliminary information about how the agent is processed by the body (pharmacokinetics) and how the agent affects the body (pharmacodynamics). Because the agents are given in such small amounts, no information is obtained about their safety and effectiveness in treating cancer. Phase 0 trials are also called "micro-dosing studies" (exploratory investigational new drug [IND trials]), or early Phase 1 trials. The people how take part in these trials usually have advanced disease and no known effective treatment options are available to them.

Phase 1:

These trials are conducted mainly to evaluate the safety of chemical or biological agents or other types of interventions (e.g., a new radiation technique). They help determine the maximum dose that can be given safely (also known as the maximum tolerated dose), and whether an intervention causes harmful side effects. Phase 1 trials enroll small numbers of patients (20 or more) who have advanced cancer that cannot be treated effectively with standard treatments or for which no standard treatment exists. Although evaluating the effectiveness of interventions is not a primarily goal of these trials, doctors do look for evidence that the interventions might be useful as treatments.

Phase 2:

These trials test the effectiveness of interventions in people who have a specific type of cancer or related cancers. They also continue to look at the safety of interventions. Phase 2 trials usually enrolled fewer than 100 people, but may include as many as 300. The people who participate in Phase 2 trials may or may not have been treated previously with standard therapy for their type of cancer. In a person has been treated previously, their eligibility to participate in a specific trial may depend upon the type or amount of prior treatment they have received. Although Phase 2 trials can give some indication of whether or not an intervention works, they are almost never designed to show whether the

intervention is better than standard therapy.

Phase 3:

These trials compared the effectiveness of a new intervention or a new us of an existing intervention with the current standard of care for a particular type of cancer. Phase 3 trials also examine how the side effects of the new intervention compare with those of the usual treatment. If the new intervention is more effective than the usual treatment and/or is easier to tolerate, it may become the new standard of care.

Phase 3 trials usually involve large groups of people (100 to several thousand) who are randomly assigned to one of two treatment groups; (1) a control group, in which everyone receives the usual treatment for their type of cancer, or (2) investigational or experimental group in which everyone in the group receives the new intervention or new use of an existing intervention. The trial participants are assigned to their individual groups by random assignment. Randomization helps insure that the groups have similar characteristics. This balance is necessary so the researchers can have confidence that any difference they observe in how the two groups respond to the treatments they receive are due to the treatments and not to other differences between the groups.

Randomization is usually done by a computer program to ensure that human choices do not influence the assignment to groups. The trial participants cannot request to be in a particular group and the researchers cannot influence how people are assigned to the groups.

People that are participating in Phase 3 trials may or may not have been treated previously. If they have been treated previously, their eligibility to participate in a specific trial may depend upon the time and amount of prior treatment they received. In most cases an intervention will move into Phase 3 testing only after it has shown promise in Phase 1 and 2 trials.

Phase 4:

These trials further evaluate the effectiveness of long-term safety of drugs or other interventions. They usually take place after a drug or intervention has been approved by the FDA for standard use. Several hundred to several thousand people may take part in a Phase 4 trial. These trials are also known as "post-marketing surveillance trials". They are generally sponsored by drug companies.

As seen by the above definitions, one can see that there is no financial implication to any of these Phases. Any Phase trial could involve free, inexpensive, or extremely expensive routine therapies that would generally be covered by the patient or third party. And, any Phase treatment could include

minimal laboratory assessment and simple relatively inexpensive monitoring studies, or on the other hand extremely expensive lab analyses and imaging studies that would be standard for that type of cancer and would ordinarily be covered by third party payers or the patient. That is why I believe that the Phases of clinical research studies cannot be used as a determinant for insurance coverage of routine care.

An example of a Phase 2 trial, just one of the 140 or so trials we have available, is NCCTG Protocol N0733, which is for metastatic breast cancer treating women with HER2 positive breast cancer previously treated with trastuzumab and anthracycline and a taxane. The standard therapy for this situation in this incurable disease would be further chemotherapy with other agents. Lapatinib is an approved second-line anti-HER2 agent. Capecitabine is one of standard salvage chemotherapies in this circumstance.

This Protocol involves capecitabine and lapatinib on a two-arm study with or without IMC-A12. This new agent is an insulin growth factor receptor inhibitor which shows great promise in breast cancer. As far as the cost is concerned, in this study, because it combines two fairly new targeted agents, lapatinib and the IMC agent are both provided free of charge for patients on the study as the lapatinib and capecitabine would be commercially available and would be covered by the patient or third party payer. Since the standard therapy that has proven most effective would be a combination of capecitabine and lapatinib, having the provision of part of the drugs on the study will save several thousand dollars a month to patients being treated on this study. The monitoring on this study would require a little more time on the patients' part to answer questionnaires and the monitoring of response to treatment would be exactly the same as patients on standard therapy. The laboratory assessment would include the addition of tests to monitor blood sugar that would be done at the same time as the patients' routine lab. This may add up to some tens of dollars per month in extra lab charges.

This would be a typical example of a Phase 2 study that either costs the same or less than standard therapy.

As far Phase 3 studies go, one of our longstanding breast cancer studies is SWOG Protocol S0221, which involves Adriamycin-Cytoxan chemotherapy followed by paclitaxel in women who have a node-positive or high-risk node-negative breast cancer. This adjuvant approach is a longstanding Phase 3 study that has treated several thousand women. The standard arm would be the every two-week Adriamycin-Cytoxan followed by weekly paclitaxel for 12 weeks. The investigational arm receives the same Adriamycin-Cytoxan treatment followed by paclitaxel every two weeks for 6 treatments. Therefore, in this study the patients' investigational therapy would require half as many treatments, although twice the dose of paclitaxel as the standard arm. Drug costs would be almost identical and the infusion costs would be slightly less for the patients on the experimental arm. Overall lab followup is the same on the

standard arm and the investigational arm. Overall the difference in cost to the patient or third parties will be minimal.

These are just two routine examples of clinical studies that we are doing in which the clinical research obviously does not involve much or any cost burden beyond standard care. If I review all our 140 current Protocols, I am sure there are some that would require some extra laboratory assessment or imaging assessment that could increase the cost slightly beyond what would be considered standard. This will be not a usual circumstance however as in the development of NCI Protocols standard acceptable monitoring costs are taken into account and extra funding provided for those studies that would not be part of routine care. It is for this reason that all biologic sample analyses, DNA testing, and tissue investigation for tumor characteristics are all funded by the studies themselves without expense to the patient or third party payers.

Sincerely,

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